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Research paper

Parameters affecting the drug release from in situ gelling nasal inserts

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Abstract

The purpose of the study was to investigate the influence of physicochemical drug properties, drug loading, and composition of the release medium on the drug release from in situ gelling nasal inserts. Sponge-like nasal inserts of carrageenan and HPMC K15M with the model drugs oxymetazoline HCl, diprophyllin, and acetaminophen (APAP) were prepared by lyophilization. Drug release studies at different drug loadings were performed in various release media. Raman analysis, DSC, and SEM were conducted to analyze the physical state of the drugs in the inserts. All drugs were dissolved in the solid HPMC inserts and were released at similar rates at all investigated loadings except for the least soluble APAP. APAP concentrations in the hydrating HPMC K15M inserts in excess of its solubility limit resulted in reduced relative release rates at higher drug loadings. Drug–polymer interactions (formation of less soluble drug–polymer salts) resulted in a slower release of oxymetazoline HCl from carrageenan inserts than from HPMC K15M inserts. Changes in the composition of the release medium affected the water uptake of carrageenan but not of HPMC K15M inserts. Oxymetazoline release from carrageenan inserts increased with higher Na^+-content of the medium because of ion exchange and at low (pH 2) as well as at high pH (pH 10). The osmolality of the release medium had no effect. The solubility of the drug, its physical state in the polymer matrix, and drug–polymer interactions governed the drug release from nasal inserts. The release from inserts prepared with oppositely charged polymers and drugs was influenced by electrostatic drug–polymer interactions and by the composition of the release medium.

Keywords: Carrageenan; Drug–polymer interaction; Extended drug release; HPMC; Inserts; Nasal drug delivery; Release medium

1. Introduction

Nasal inserts have previously been described as a promising drug delivery system [1–3]. This solid dosage form, which is prepared by lyophilization, consists of a sponge-like hydrophilic polymer matrix, in which the drug is embedded. It allows easy dosing with a high potential for systemic administration under circumvention of the harsh conditions of the gastrointestinal tract and the hepatic first pass metabolism [4]. Once in contact with the highly vascularized nasal mucosa, the polymer sponge takes up water and rapidly forms a gel from which the pharmaceutically active ingredient is released in a controlled fashion. The use of bioadhesive polymers ensures a prolonged nasal residence time for extended release application.

Although the nasal mucosa allows the delivery of higher molecular weight drugs, such as proteins and DNA [5–8] low molecular weight model drugs were used in the present study to elucidate the embedding of the drug in the polymer matrix, possible drug–polymer interactions, and the release mechanism.

Besides the properties of the drug and the delivery system, the physiological conditions of the nasal cavity can also influence the performance of the system. The pH of the nasal fluid is normally around 5.5–6.5 but depends on air temperature, sleep, emotions, and food ingestion [9,10]. An increase in pH to 7–9 during acute and allergic rhinitis, rhinirhea, and chronic and acute sinusitis was observed [11,9]. Also diabetes mellitus influences the nasal

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pH [12]. Inhalation of cold, dry air can act as a physical stimulus to induce symptoms of rhinitis that are associated with an increase in osmolality from 280 to 290 to ≈310 mosm/kg [13]. Stimulation of the nasal gland secretion with chilli powder was reported by [14] to reduce the osmolality to approximately 238 mosmol/L. The same authors also found changes in the sodium and potassium ion content of the nasal secretion. Pathological conditions also affect the viscosity and viscoelasticity of the nasal mucus as well as the ciliary beat frequency [15,16].

The variability in the composition and properties of the nasal fluid can greatly influence the performance of a nasally administered drug delivery system [4,17].

Besides the effect of the drug properties (molecular weight, solubility, and drug–polymer interaction) and drug loading, this study also investigated the influence of the release medium (osmolality, sodium ion content, and pH) on water uptake and drug release properties of in situ gelling nasal inserts.

2. Materials and methods

2.1. Materials

Model drugs: oxymetazoline hydrochloride (Procter & Gamble Pharmaceuticals Germany, Weiterstadt, Germany); diprophyllin (Knoll AG, Ludwigshafen, Germany); acetaminophen (APAP, Synopharm GmbH, Barsbüttel, Germany). Polymers: ι-carrageenan (Genuvisco carrageenan type TPH-1, Copenhagen Pectin A/S, Lille Skensved, Denmark); hydroxypropyl methylcellulose (HPMC, Methocel K15M, Colorcon Ltd., Dartford, UK). All other excipients were of pharmaceutical grade. Purified water was used as a solvent if not otherwise stated.

2.2. Insert preparation

Polymers (2% w/w) and drug (5%, 10%, 20%, 30%, 40%, 50%, 60%, and 100% on polymer mass, w/w) were dissolved in purified water. Aliquots ($V = 1.5$ or 0.1 ml) were placed into blister molds and frozen at −25 °C for 1 h. The samples were then freeze-dried (0.25 mbar for 24 h with increasing shelf temperature −15 to 0 °C and a final drying for 2 h at +15 °C and 0.01 mbar) (Gamma 2-20, Martin Christ Gefriertrocknungsanlagen GmbH, Osterode am Harz, Germany). The inserts were stored in a desiccator until use.

2.3. Water uptake

A sponge (5 cm × 6.5 cm × 3 cm, Santex household sponge, Santex GmbH, Wald-Michelbach, Germany) was fully soaked in the hydration medium (phosphate buffer, pH 6.0, USP XXVII) and placed in a petri dish filled with the same buffer to a height of 1 cm in order to keep the sponge soaked during the experiment. Round filter paper ($d = 55$ mm, Schleicher & Schuell GmbH, Dassel, Germany) was also soaked in the medium and positioned on top of the sponge. This experimental set-up was equilibrated for 30 min. Accurately weighed inserts ($V = 1.5$ ml) were then placed on the filter paper and the water uptake was determined as weight increase of the insert (weight of hydrated insert and filter paper minus weight of wet filter paper) over time normalized to the initial dry insert weight ($n = 3$).

Different buffers were used as medium. For the investigation of the effects of medium composition, phosphate buffer, pH 6.0 (USP XXVII), was adjusted to the chosen osmolality by addition of sorbitol (Osmomat 030, Gonotec Gesellschaft für Meß- und Regeltechnik mbH, Berlin, Germany). Sodium ion content was adjusted by addition of sodium chloride. Alkaline borate buffer, pH 10 (USP XXVII), and hydrochloric acid buffer, pH 2 (USP XXVII), were used with the necessary adjustments of osmolality and sodium ion content. The potassium ion content was constant at 0.05 mol/L in all buffers and no other positively charged ions were present.

2.4. In vitro drug release

A self-made diffusion cell was used for drug release studies mimicking the humidity properties of nasal mucosa. It consisted of a release medium container (20–80 ml phosphate buffer, pH 6.0, USP XXVII) into which a tube of 3.5 cm inner diameter was inserted. The lower end of the tube was closed with a tightly stretched, thin sponge and adjusted exactly to the height of the release medium surface so that the sponge was wetted but not submersed. Inserts ($V = 1.5$ ml) were placed on the thin sponge and the whole system was closed with Parafilm® "M" sealing film (American National Can Company, Chicago, IL, USA) to avoid evaporation of release medium and to allow the establishment of a constant relative humidity around the insert. The experiments were performed in a horizontal shaker with 75 rpm and at 37 °C. Samples of 2 ml were taken at predetermined time points and replaced by fresh medium. The drug content of the samples was analyzed by UV spectrophotometry (oxymetazoline HCl: $\lambda = 280.0$ nm, diprophyllin: $\lambda = 273.5$ nm, and APAP: $\lambda = 243.6$ nm, UV-2101 PC, Shimadzu Deutschland GmbH, Duisburg, Germany). Drug-free inserts were also subjected to the drug release test to quantify the contribution of the polymers to the UV-absorption. At each time point this value was subtracted from the value of the drug-loaded inserts. The actual drug loading of the inserts was determined by complete dissolution of inserts in phosphate buffer, pH 6.0 (USP XXVII), followed by UV analysis. The contribution of the polymers to the UV-absorption was substracted. All drug release experiments were performed in triplicate (mean ± SD) and under sink conditions ($c_{\max \text{ in medium}} < 10\%\ c_{\text{saturation}}$).

2.5. Raman spectroscopy

Carrageenan and oxymetazoline HCL powders were analyzed in a capillary while the inserts (carrageenan 2%

w/w loaded with oxymetazoline HCl 20%, w/w based on polymer mass) were compressed for measurements. A FT-Raman-spectrometer with an integrated, software-controlled Nd:YAG-Laser ($\lambda = 1064$ nm, RFS 100, Bruker Optik GmbH, Ettlingen, Germany) was employed for the recording of the Raman spectra. The theoretical spectrum, calculated by fractional addition of the spectra of the single substances, was compared to the measured insert spectrum.

2.6. Differential scanning calorimetry

Films were cast from polymer solutions (carrageenan or HPMC K15M 2% w/w with increasing amounts of diprophyllin or APAP, % w/w based on polymer mass), dried at 60 °C, and stored in a desiccator until use. The turbidity of the films was observed visually by comparison with a drug-free film of the same polymer. A computer-interfaced differential scanning calorimeter (DSC 821, Mettler Toledo AG, Gießen, Germany) was used to determine the crystalline drug content in films. The film samples were accurately weighed and heated from 20 to 190 °C at a rate of 10 K/min. The presence of an endothermic peak around the melting point of the pure drug (Table 1) was used as a marker of crystalline drug and the enthalpy of melting/sample mass was determined. A linear correlation between the melting enthalpy/sample mass and the drug content of the film was established and extrapolation to enthalpy/sample mass = 0 gave the "solubility" of the drug (absence of crystalline drug) in the film matrix.

The crystalline oxymetazoline HCl content of polymer films could not be determined by this method because the drug did not melt but decomposed at 300–303 °C.

2.7. Scanning electron microscopy

Inserts were cut with a razor blade to expose the inner structure, fixed on a sample holder with double-sided tape, and coated for 70 s under an argon atmosphere with gold-palladium (SCD 040, Balzers Union, Lichtenstein), and were then observed with a scanning electron microscope (PW 6703/SEM 515, Philips Electronics N.V., Eindhoven, The Netherlands) in order to detect any presence of drug crystals.

3. Results and discussion

Ideally, a particular drug delivery system should be able to perform with a wide variety of drugs with broad physicochemical properties. Therefore, the present study investigated the release of different model drugs from in situ gelling nasal inserts, which were prepared from drug-containing aqueous polymer solutions by lyophilization. The effect of type of drug and drug loading as well as the embedding of the drug in the polymeric structure were studied and related to the observed release behavior. Three low molecular weight model drugs – oxymetazoline hydrochloride, diprophyllin, and acetaminophen (APAP) – with different physicochemical properties were chosen (Table 1). Two polymers, HPMC K15M (neutral) and carrageenan (anionic), were evaluated as carrier materials.

3.1. Effect of drug species and drug loading

Despite the differences in drug solubility and pK_a (Table 1), no differences in drug release were seen for the three drugs at a 5% loading (w/w based on polymer mass) with inserts prepared from HPMC K15M, a high molecular weight, uncharged cellulose derivative (Fig. 1A). This indicated that the drug release from HPMC K15M inserts was controlled mainly by diffusion of dissolved drug.

In contrast to HPMC K15M, carrageenan is a negatively charged polysaccharide. The drug species diprophyllin and APAP, which are neutral at pH 6, were released at a similar rate from the carrageenan inserts, while oxymetazoline HCl was released slower (Fig. 1B). This drug is a weak base and carries a positive charge at pH 6. Thus, it was able to interact with the anionic carrageenan. This interaction led to the observed apparent zero-order-release kinetics. Similar observations were described by [18] for chitosan (a cationic polysaccharide) films loaded with the anionic drug salicylic acid.

Precipitation studies showed the formation of an insoluble oxymetazoline/carrageenan salt in concentrated solutions. During hydration of the solid insert, the drug and polymer dissolve and can thus form the insoluble salt. Oxymetazoline–carrageenan salts were investigated by Raman spectroscopy, which showed a peak shift from 1568 to 1578 cm^{-1} (region 1490–1580 cm^{-1} representative of the secondary amino group of the drug) (Fig. 2). In addition, the peak at 1188 cm^{-1} was missing in the spectrum of the drug-loaded inserts (region 1150–1260 cm^{-1} representative for the sulfate group of the polymer). This indicated mutual interactions of these functional groups.

Next, the effect of drug loading on the drug release and the physical state of the drug in the solid inserts was investigated in order to explain the release mechanism.

The release of the three drugs from the HPMC inserts was almost independent of the drug loading (5–50%), the

Table 1
Physicochemical properties of the model drugs

Drug	MW	Solubility in water (mg/ml)	pK_a	Melting point (°C)
Oxymetazoline HCl	297 (262 w/o Cl^-)	149	9.9 (weak base)	300–303 (decomposition)
Diprophyllin	254	330	–	158
APAP	151	14	9.5 (weak acid)	169–171

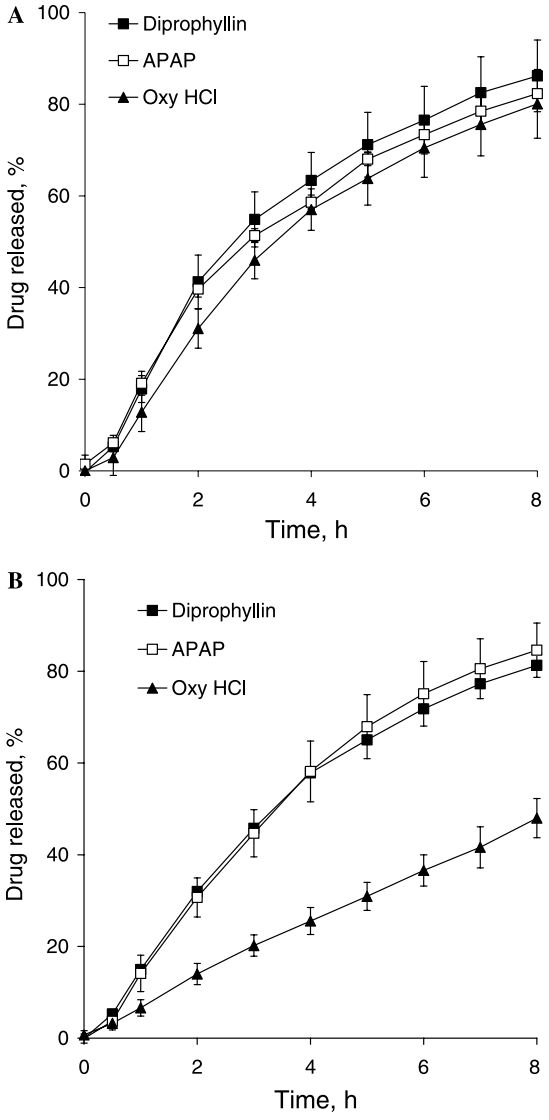

Fig. 1. Release of diprophyllin, APAP, and oxymetazoline HCl from (A) HPMC K15M and (B) carrageenan inserts (polymer, 2% w/w; drug, 5% w/w based on polymer mass).

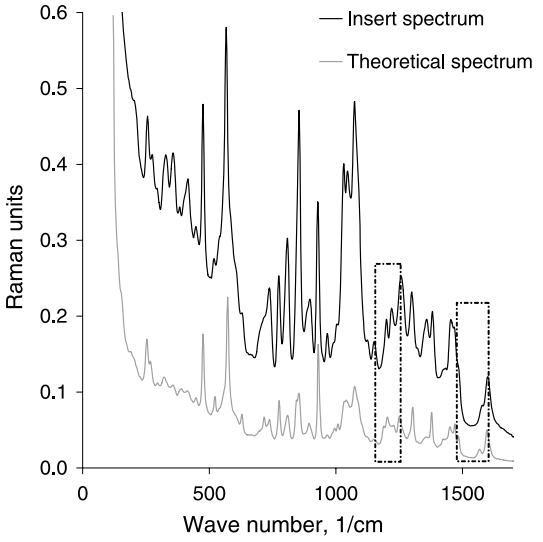

Fig. 2. Raman spectrum of carrageenan inserts loaded with oxymetazoline HCl (polymer, 2% w/w; drug, 20% w/w based on polymer mass) in comparison to the theoretical spectrum calculated from the single substances.

release decreasing slightly with the least soluble APAP with increasing APAP loading (Figs. 3A–C). With carrageenan inserts, the release of the uncharged diprophyllin and weak acid APAP was also independent of drug loading (5–40%) (Figs. 3G and H), while the release of the weak base oxymetazoline HCl was clearly influenced by the drug loading due to formation of the poorly soluble drug–polymer salt and decreased with increasing drug loading (Fig. 3I).

The slightly reduced release rate of APAP from HPMC K15M inserts at higher loadings was attributed to its lower aqueous solubility compared to the other two drug species (Table 1). Based on water uptake (Fig. 4A), polymer mass loss during hydration due to polymer dissolution and drug release studies, the concentration of the remaining drug in the hydrated insert was calculated. For simplicity, a homogeneous distribution of the water within the insert during hydration was assumed for this calculation, although visual observations of the inserts showed that the absorbed water was, at least initially, not homogeneously distributed in the inserts. The concentration of APAP in the carrageenan inserts was reduced below the drug solubility for all drug loadings within 3 h (Fig. 4C) corresponding to approximately 40% drug release (Fig. 3H). Although APAP was not completely dissolved in the hydrated insert in the beginning of the release test, the drug was completely dissolved during the major part of the release study and could diffuse freely. This resulted in a drug release from carrageenan inserts, which was independent of the drug loading (Fig. 3H).

HPMC K15M inserts, on the other hand, took up much less water during hydration studies and the local APAP concentration was therefore higher (Figs. 4A and B). The drug concentration dropped below solubility at <0.5 h at a drug loading (w/w based on polymer mass) of 5%, at ~1.75 h for 10%, at ~3.75 h for 20%, at ~5.5 h for 30%, and at ~8 h for 50% (Fig. 4B). White spots of undissolved APAP were observed in the gel matrix after 8 h of drug release with the highest drug-loaded inserts (50% loading). The maintenance of a depot of undissolved drug over a long time of the drug release study resulted in the reduced APAP release rate from HPMC K15M inserts (Figs. 3C and 4B). In direct comparison with the freely water soluble drugs diprophyllin and oxymetazoline HCl, the reduced APAP release rate from HPMC K15M inserts became clearly visible at the 50% drug loading compared to the 10% and 20% loadings (Figs. 3D–F).

Neither diprophyllin nor oxymetazoline HCl resulted in local drug concentrations in HPMC K15M and carrageenan inserts during the drug release test that exceeded the aqueous solubility of the drugs.

Besides the investigation of the drug solubility in hydrated inserts, the physical state of the drug in films and inserts

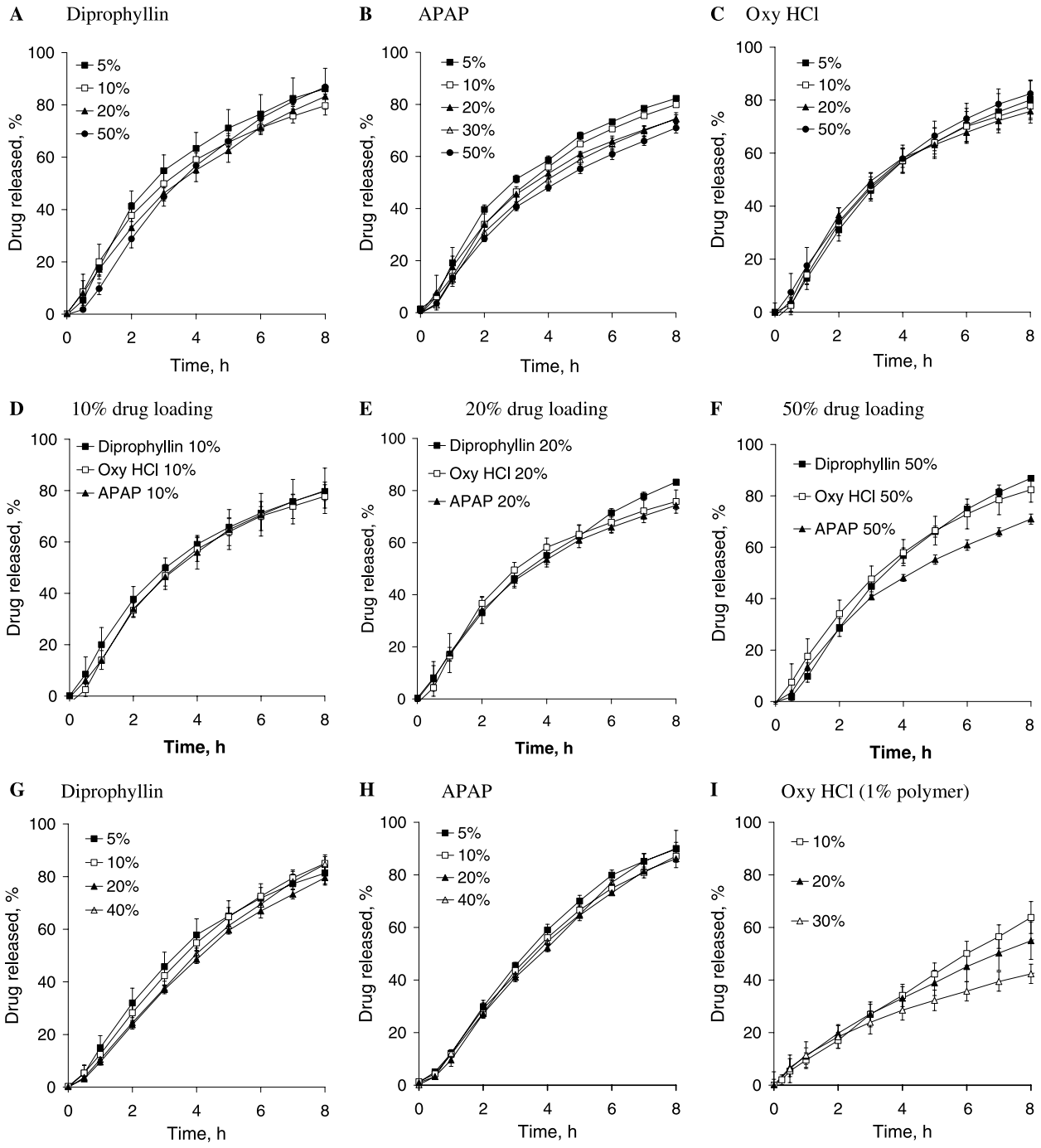

Fig. 3. Release of diprophyllin, APAP, and oxymetazoline HCl from (A–F) HPMC K15M and (G–I) carrageenan inserts with different loadings (polymer, 2% w/w).

was also investigated to explain the observed drug release behavior. The drug could be either dissolved or dispersed in amorphous or crystalline form in the solid polymer matrix after the lyophilization of the drug–polymer solutions into the solid inserts. Visual observation of cast films, DSC measurements, and scanning electron microscopy were used to characterize the physical state of the drug in films and inserts (Table 2). Films of the pure polymers were clear. Clear drug-containing films roughly indicated that the drug was dissolved in the matrix, while turbid films indicated the presence of dispersed drug.

As already expected because of the turbidity of carrageenan/oxymetazoline HCl solution, the resulting films were turbid because of the formation of the poorly water soluble salt. DSC studies could not be performed with oxymetazoline HCl due to thermal degradation. SEM revealed no crystals in carrageenan inserts loaded with less than 40% drug (Table 2). As previously described, the poorly water

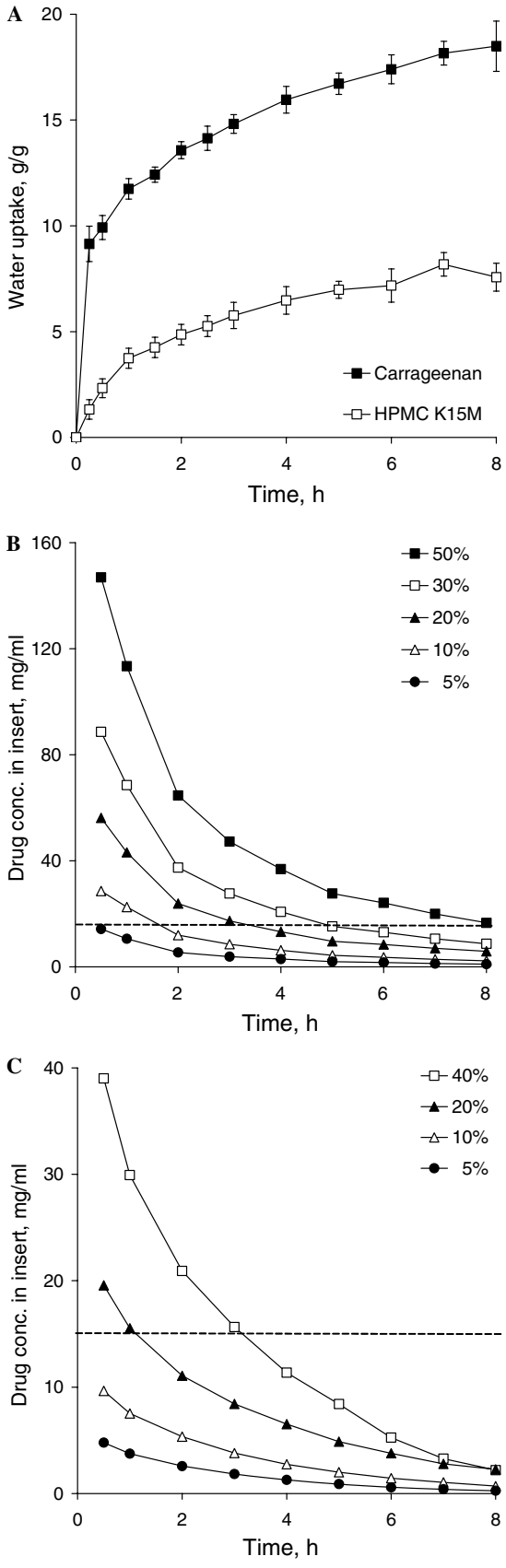

Fig. 4. (A) Water uptake (polymer, 2% w/w; 22 °C) and theoretical drug concentration in the hydrating (B) HPMC K15M and (C) carrageenan inserts with different loadings of APAP (polymer, 2% w/w) (dotted line represents aqueous solubility of drug).

soluble oxymetazoline/carrageenan salt determined the extended drug release behavior of these inserts.

Film turbidity at $\geqslant 10\%$ and crystalline drug (DSC) at $\geqslant 49\%$ (w/w based on polymer mass) in carrageenan/diprophyllin films indicated the presence of amorphous drug within this loading range (Table 2). Due to the high water solubility of diprophyllin, its physical state in the inserts may be less important for the drug release. The formation of diffusible drug by dissolution of either the solid polymer/drug solution (<10%) or the solid drug alone (amorphous <49% or crystalline $\geqslant 49\%$) occurred very rapidly.

Carrageenan/APAP films contained the drug in crystalline form (film turbidity and crystallinity (DSC) at $\geqslant 5\%$ drug) (Table 2). The crystalline state of APAP was maintained over the entire loading range tested; an effect of the physical state of APAP on the release from carrageenan inserts could therefore be excluded. The solubility of the APAP crystals determined the release. Studies on local APAP concentration already showed that the water taken up by the carrageenan inserts was sufficient to dissolve the APAP after an initial phase (Fig. 4C).

In HPMC K15M films, the three drugs were dissolved in the polymer matrix: APAP up to ~37% loading, diprophyllin up to ~48%, oxymetazoline HCl up to >40% (Table 2). The dissolved state of all three drugs in HPMC K15M resulted in a similar drug release of all three drugs up to 20% loading (Figs. 3D and E). The hydration of the polymer matrix led to the release of diffusible drug without a prior step of dissolution of dispersed drug. At 50% drug loading (w/w based on polymer mass), only APAP was significantly present in crystalline form (Table 2). At this loading, not only the matrix hydration but, more importantly, the dissolution of the drug crystals determined the release. This resulted in a lower drug release rate for APAP compared to diprophyllin and oxymetazoline HCl from HPMC K15M inserts (Fig. 3F).

In summary, the release mechanism of drugs from nasal inserts was determined by the local solubility of the drug in the hydrated inserts and thus the physical state of the incorporated drug. The physical state of the drug in the nasal inserts (i.e., dissolved vs. undissolved) may change with increasing drug loading of the inserts.

3.2. Effect of the composition of the release medium

The performance of a drug delivery system does not only depend on its composition and structure but also on the physiological conditions at its site of administration. The nasal fluid varies in pH, ion content, and osmolality; this could affect the performance of in situ gelling nasal inserts. Thus, further studies were conducted to investigate the influence of the release medium on the oxymetazoline HCl release from and the water uptake of in situ gelling nasal inserts.

The osmolality of the release medium was adjusted by sorbitol addition; the ion content in media of different osmolality kept constant. The osmolality of the medium

Table 2
Summary of the physical state of different model drugs in carrageenan and HPMC K15M films and inserts with different drug loading (% w/w based on polymer mass) (2% polymer)

Polymer/drug	Film turbidity (%)	DSC/inserts (crystalline drug) (%)	SEM/inserts (visible drug crystals) (%)
Carrageenan/Oxy HCl	⩾5	n.p.	⩾40
Carrageenan/APAP	⩾5	5	n.p.
Carrageenan/Dipro	⩾10	49	n.p.
HPMC K15M/Oxy HCl	n.d. up to 100	n.p.	n.d. up to 40
HPMC K15M/APAP	⩾40	37	n.p.
HPMC K15M/Dipro	⩾60	48	n.p.

n.d., not detectable; n.p., not performed.

did not influence the water uptake and the drug release from both polymer inserts (Figs. 5A–D). Effects at higher osmolalities cannot be excluded, however they are irrelevant for physiological and pathophysiological conditions.

The Na^+-concentration of the medium had no effect on water uptake and drug release from HMPC K15M inserts due to the neutral character of HPMC (Figs. 6A and B). Carrageenan inserts were strongly affected by the Na^+-concentration of the medium. The water uptake was reduced with increasing Na^+-content of the medium (Fig. 6C). This was attributed to the formation of a stronger gel with a higher viscosity. The enhancing effect of various cations on carrageenan gelling properties has been described [19]. A gel with increased viscosity can act as a diffusion barrier for water uptake. The reduced water uptake, however, was not mirrored by the oxymetazoline release from carrageenan inserts. In contrast, the drug release was enhanced with increasing amounts of sodium ions (Fig. 6D). This phenomenon was related to the previously mentioned ionic interaction between oxymetazoline HCl and carrageenan. Na^+ replaced oxymetazoline at the sulfate group of the polymer. Higher Na^+-concentrations led to a more quantitative ion exchange of oxymetazoline and thus to a faster drug release. Similar observations had previously been made by [20] for chlorpheniramine maleate-loaded carrageenan tablets.

The pH of the medium did not affect the water uptake and drug release of HPMC K15M inserts (Figs. 7A and B). This was again attributed to the absence of charged groups in the polymer. In contrast, the sulfate groups

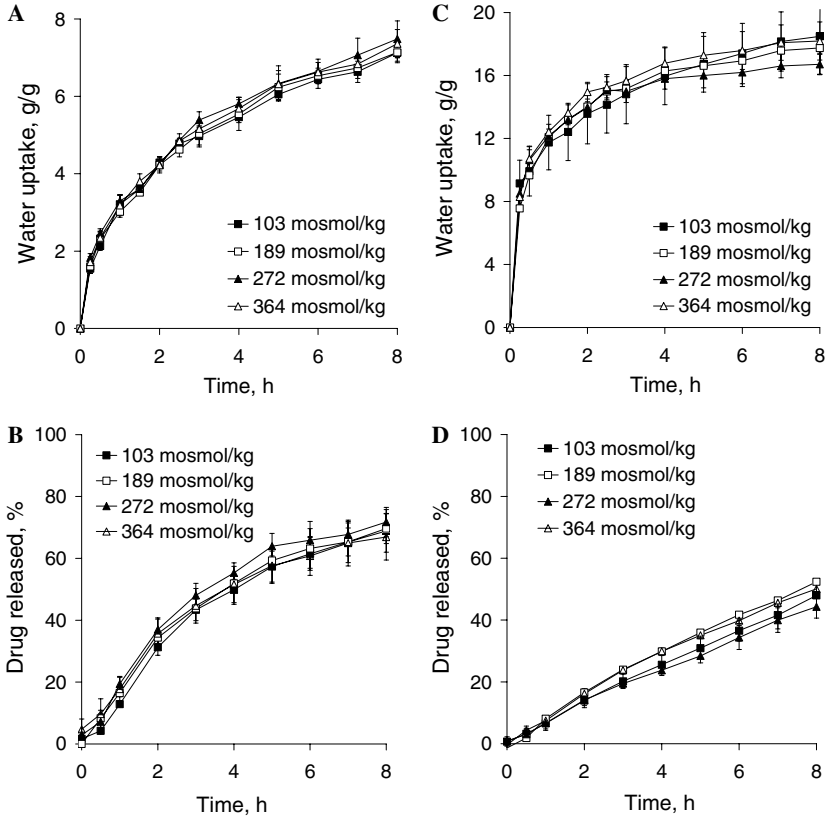

Fig. 5. Effect of osmolality of release medium on (A and C) water uptake (22 °C) and (B and D) oxymetazoline HCl release (37 °C) of (A and B) HPMC K15M and (C and D) carrageenan inserts (polymer, 2% w/w; drug, 5% w/w based on polymer mass, pH 6, $[Na^+] = 0.005$ mol/L).

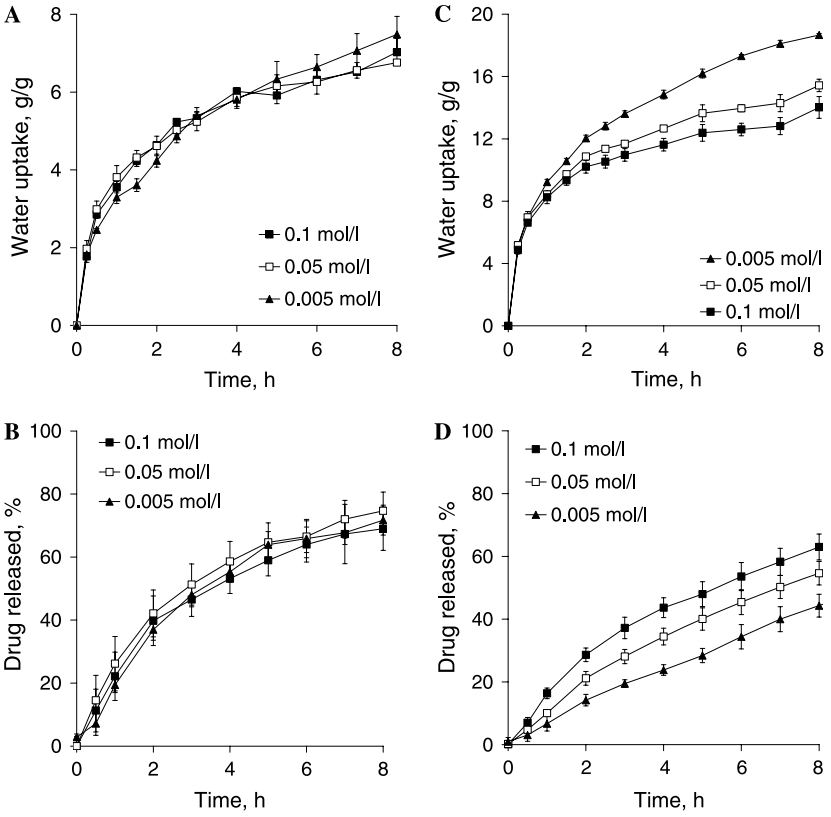

Fig. 6. Effect of Na^+-concentration of release medium on (A and C) water uptake (22 °C) and (B and D) oxymetazoline HCl release (37 °C) of (A and B) HPMC K15M and (C and D) carrageenan inserts (polymer, 2% w/w; drug, 5% w/w based on polymer mass, pH 6, 272 mosmol/kg).

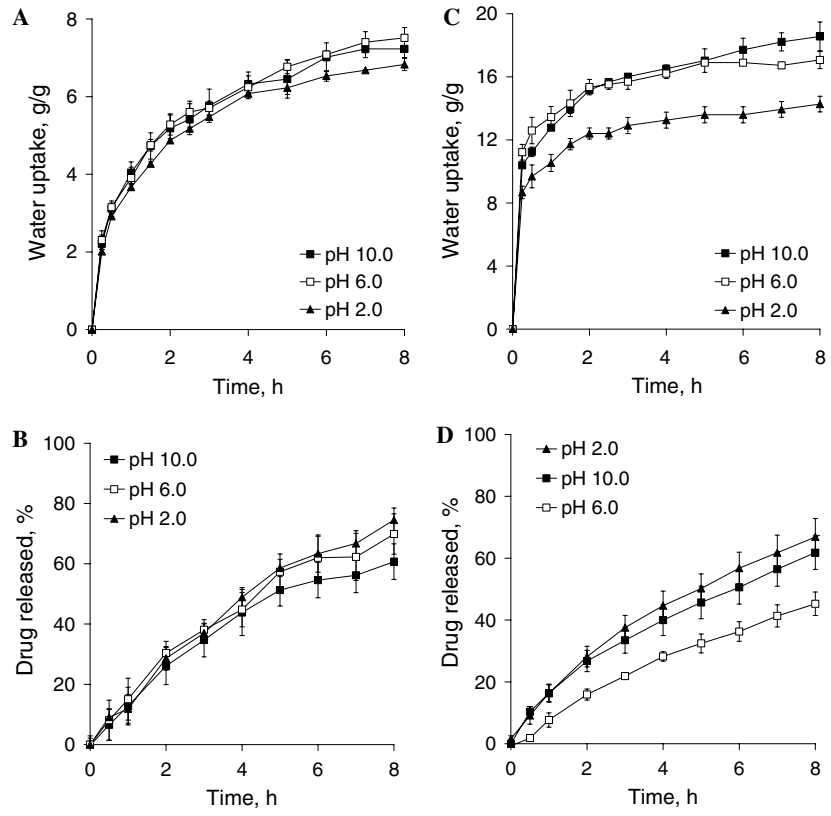

Fig. 7. Effect of pH of release medium on (A and C) water uptake (22 °C) and (B and D) oxymetazoline HCl release (37 °C) of (A and B) HPMC K15M and (C and D) carrageenan inserts (polymer, 2% w/w; drug, 5% w/w based on polymer mass, 272 mosmol/kg, $[Na^+] = 0.044$ mol/L).

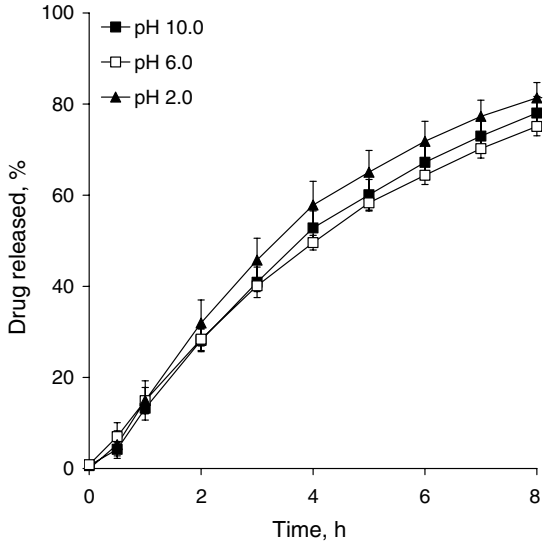

Fig. 8. Effect of pH of release medium on diprophyllin release from carrageenan inserts (polymer, 2% w/w; drug, 5% w/w based on polymer mass, 272 mosmol/kg, $[Na^+] = 0.044$ mol/L).

(pK_a 1–2) of carrageenan were sensitive to pH-changes. At pH 2, at least some of the groups were protonated and therefore neutralized. This reduced the osmotic pressure in the hydrating insert, resulting in a lower water uptake at pH 2 compared to pH 6 and 10 (Figs. 7C). The release of the weak base oxymetazoline HCl from carrageenan inserts at different pH was governed by the ability of the insert components to interact electrostatically (Fig. 7D). As previously discussed, carrageenan was partly neutralized at pH 2, while pH 10 led to the formation of oxymetazoline-free base. In both pH media, the electrostatic interactions between drug and polymer were weakened due to partial neutralization of charges. This resulted in a faster drug release. The free oxymetazoline base formed at pH 10 has a lower solubility in water than the hydrochloride salt and could thus retard the drug release. However, this was not observed, indicating that the solubility limit of the drug base was not exceeded either due to sufficient water uptake by the inserts or due to a partial neutralization only (pK_a 9.9 and pH 10, thus only about 50% of the drug existed as free base). At low pH, acid-catalyzed hydrolysis of carrageenan may also contribute to the increased drug release rate. However, this is known to occur only in the dissolved state, but not in the gelled state as present during water uptake and drug release studies performed in this study [21]. In contrast, both species were fully charged at pH 6, leading to the slowest release rate due to stronger drug–polymer interactions.

No differences in drug release in different pH media were found with the neutral drug diprophyllin; the charge of the polymer was not relevant for the release of a neutral drug (Fig. 8).

Effects of release medium properties on the drug release from the nasal inserts depend on the polymer and the incorporated drug and were observed especially with respect to pH and Na^+-content. The relevance for in vivo performance for the studied model drugs is fairly low because effects were seen at rather extreme conditions (e.g., pH 2 and pH 10). However, significant in vivo effects may result when considering drugs with pK_a-values within the physiological and pathophysiological pH of the human nose.

4. Conclusion

The drug release of low molecular weight drugs from in situ gelling nasal inserts was influenced primarily by: (i) the solubility of the drug, (ii) the physical state of the drug in the polymeric inserts, and (iii) electrostatic interactions between drug and polymer. The physicochemical properties of the drugs will therefore play a significant role in nasal drug delivery via nasal inserts.

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